DETAILED ACTION

1. Claims 138-152 are currently pending in the instant application.

Response to Amendment

2. Applicants' Amendment and Response, submitted June 9, 2011, has been reviewed by the Examiner and entered of record in the file. Accordingly, claims 140, 141 and 143 have been amended, and new claims 146-152 have been added.

Previous Rejections

3. Claim 140, 141 and 143 previously rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification, while being enabling for methods for treating diseases such as asthma, inflammation, COPD, certain dermatological conditions, etc., does not reasonably provide enablement for the "laundry list" of diseases recited in claim 140, or for the prevention of said diseases. The Examiner notes with appreciation Applicants' deletion of the term "prevention" from the claims, and amendment of claim 140 in order to limit the scope of the diseases encompassed. However, the claim still recites "inflammatory diseases" which covers an extremely broad number of conditions or diseases not enabled by the disclosure. New claims 146 and 150 recite treating multiple sclerosis, and inflammatory disease, respectively. Therefore the rejection is maintained regarding claim 140, and applied to new claims 146 and 150.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described in the previous Office Action.

The nature of the invention

Claim 140 recites, "A method of treating at least one condition selected from ... inflammatory diseases... comprising administering to the subject the composition of claim 138 in an amount sufficient for treating the at least one condition." The nature of the invention in claims 140, 146 and 150 is methods for the treatment of diseases involving the dipeptidyl peptidase IV and aminopeptidase enzymes.

The Breadth of the Claims and

The State of the Prior Art

The applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." MPEP §2163(II)(1), *In re Morris*, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Disorders associated with inflammation comprise a large, officially unrelated group which underlie a broad variety of human diseases. The immune system is often involved with inflammatory disorders, demonstrated in both allergic reactions and some myopathies, with many immune system disorders resulting in abnormal inflammation. Other diseases with etiological origins in inflammatory processes are thought to include cancer, atherosclerosis, and ischaemic heart disease. Examples of disorders associated with inflammation include: Acne vulgaris, Asthma, Autoimmune diseases, Chronic prostatitis, Glomerulonephritis, Hypersensitivities, Inflammatory bowel diseases, Pelvic inflammatory disease, Reperfusion injury, Rheumatoid arthritis, Sarcoidosis, Transplant rejection, Vasculitis, Interstitial cystitis, etc, which covers an extremely broad spectrum of diseases/disorders that are difficult to predict and treat.

Similarly, at the time of this application, although there had been substantial progress reported in the scientific literature about the multiple etiologies of multiple sclerosis, including genetic makeup and environmental factors, multiple sclerosis remains a "difficult disease for which solutions seem attainable yet remain elusive." See **Compston, A.**, and **Coles, A.,** "Multiple sclerosis," The Lancet, vol. 359, pages 1221 – 1231 (April 6, 2002), at page 1224, col. 2, lines 21, et seq. (describing various causes of multiple sclerosis); page 1226, lines 10 et seq. (treatment of multiple sclerosis with β-interferons and synthetic amino acid polypeptides, corticosteroids, etc.), and page 1221, lines 18 – 36 (elusiveness of treatments to treat multiple sclerosis); see also, **Hartung, H., et al.**, "What do we know about the mechanism of action of disease-modifying treatments in MS?" J. Neurol., vol. 251(suppl. 5), pages V/12 – V/29 (2004), at pages V/13, lines 26 - 30 ("even without taking into account the existence of inter-patient heterogeneities, the network of factors that contribute to the pathology and pathogenesis of MS is far from straightforward"); see pages V/15 at lines 12 et seq. (role of cellular mediators such as TNF). At the time of this application, the role of "inflammation" in the development of multiple sclerosis was believed to have both *beneficial* and *detrimental* effects. Id. at p. V/16, col. 2, lines 3 – 10 ("Although it is clear that inflammation can have extremely destructive effects [on the course of multiple sclerosis], there is also evidence to suggest that inflammatory reactions may also have beneficial effects that contribute to protective or repair responses").

The level of skill in the art

Practitioners in this art (medical clinicians, pharmacists and/or pharmaceutical chemists) would presumably be highly skilled in the art for treatment of persons with the claimed diseases. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment

of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The predictability or lack thereof in the art

Because of high level of unpredictability associated with the treatment of certain inflammatory diseases such as autoimmune, cancer, etc, and Multiple Sclerosis, a greater amount of evidentiary support is needed to fully satisfy the requirement of 35 U.S.C 112, first paragraph. A survey of scientific literature indicates that the etiologies or mechanisms of those diseases or conditions known to involve aminopeptidase or dipeptidyl peptidase production, such as Alzheimer's disease and Multiple Sclerosis, were not completely understood or settled at the time of the application. As a result, the art had few benchmarks by which to measure the effectiveness of inhibitors of aminopeptidase or DPPIV inhibitors in treating such diseases.

In re Fisher, 427 F.2d 833, 839; 166 USPQ 18, 24 (CCPA 1970) held that, "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." In other words, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. The nature of the pharmaceutical arts is such that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability, even in view of the high level of skill in the art. This unpredictability is more pronounced where the diseases and conditions disclosed in the Specification are as complex and diverse as autoimmune diseases such as multiple sclerosis. It is noted that pharmaceutical art is unpredictable, requiring each

embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue.

The amount of direction or guidance present and

The presence or absence of working examples

The present application does provide *in vitro* data showing inhibition of alanyl aminopeptidase and dipeptidyl peptidase IV activity, by selected compounds of the present invention. (See Specification at pages 24- 51, Examples 1-4). Specifically, the application discloses experimental data that the instant compounds are effective for inhibiting levels of alanyl aminopeptidase and dipeptidyl peptidase in mice. However, the current claims encompass methods of treating diseases such as neurodegenerative disorders and intellectual impairment disorders, using the compounds described in the specification. The compounds disclosed in the specification, which have data regarding the claimed compounds' affinitv of the dipeptidyl peptidase IV and alanyl aminopeptidase enzymes, have no pharmacological data regarding the treatment of any and all inflammatory diseases or multiple sclerosis.

A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that compounds fall within the scope of a claim will possess the alleged activity. See *In re Riat* et al. (CCPA 1964) 327 F2d 685, 140USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724. The instant specification at most only provides processes of preparation. In the absence of such information, a person of ordinary skill in the art would reasonably require an undue quantity of experimentation even to select which patients with which specific diseases or conditions could benefit (i.e., would be "treated"), from which

composition of Formula (I) would be useful to treat diseases as diverse and complex as multiple sclerosis, and the broad spectrum of diseases/disorders covered by "inflammatory diseases."

The quantity of experimentation needed

A person of skill in the art would require an undue quantity of experimentation even to select which of the broad array of inflammatory diseases and conditions claimed in Claims 140 and 150 could be treated [see "Breadth of Claims" section], and given the complexity and diversity of multiple sclerosis of claim 146, as well as the lack of established benchmarks in the art known at the time of this application where such diseases were treated by pharmaceutical compositions. In addition, the highly-unpredictable nature of treating complex diseases involving Aβ-peptide production with compounds shown only to have DPP IV inhibitory activity, and the absence of specific guidance or working examples disclosed in the claims or Specification, would cause a person of ordinary skill in the art to perform an undue quantity of experimentation even to determine whether the instant claimed compound would be useful to treat the vast array of disorders and conditions encompassed by "inflammatory diseases," and multiple sclerosis, with no reasonable expectation of success.

It is suggested to cancel claim 146, drawn to treating multiple sclerosis, and to delete the phrases "inflammatory disease" and "inflammatory reaction" from the claims.

Claim Objections

4. Claims 147-149, 151 and 152 are objected to as being dependent on a rejected base claim.

Conclusion

5. In conclusion, claims 138-152 are currently pending, and claims 140, 146 and 150 are rejected. Claims 147-149, 151 and 152 are objected to, and claims 138, 139 and 141-145 appear allowable over the art of record.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JANET L. COPPINS whose telephone number is (571)272-0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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